Remarks

Claims 1-11 are pending in this application. Claim 12-15 were previously cancelled. Claims 3 and 5 are currently withdrawn from consideration. Claim 2 is cancelled by the amendment herein.

Claims 1, 6, 8, 10, and 11 have been amended to replace the phrase "AT binding partner" with "thrombin." Claim 1 is further amended to replace the phrase "interfering factor" with "one or more pharmaceutical compounds that inhibit thrombin." That amendment finds support at paragraphs [0022]-[0024] of the application as originally filed. Claim 1 is further amended in the first line to correct "method of detecting" to "method of determining … the content," to be consistent with the language in clause (e) of the claim. Other amendments have been made to comply with the Examiner's requirements, as explained more fully below. It is respectfully submitted that these amendments are sufficient to place the claims in condition for allowance.

The rejections are addressed in the order in which they were presented in the November 19, 2008 Office Action.

Rejections Under 35 U.S.C. § 112, First Paragraph

The claims are rejected under 35 U.S.C. § 112, first paragraph, for use of the word "excess." Claim 1 has been amended to delete the word "excess," such that this ground of rejection is overcome.

The claims are rejected under 35 U.S.C. § 112, first paragraph, for use of the phrase "such that the interfering factor is no longer available to interfere with the AT." Claim 1 has been amended to delete that phrase, such that this ground of rejection is overcome.

The claims are rejected under 35 U.S.C. § 112, first paragraph, written description requirement at paragraph 8, pages 5-9 of the present action (identical to the text of the same rejection at pages 3-7 of the Office Action of February 5, 2008); the Examiner's response to applicant's arguments is at paragraph 18, pages 16-18.

As noted above, claims 1, 6, 8, 10, and 11 have been amended to delete the phrase "AT binding partner" and replace it with "thrombin;" and to delete the phrase "interfering factor" and replace it with "one or more pharmaceutical compounds that inhibit thrombin." The recitation of

"chromogenic substrates" in claim 4 has been modified to recite that the substrate is a peptide substrate for thrombin. This amendment finds support at paragraph [0012] of the application as originally filed. It is respectfully submitted that these amendments are sufficient to comply with the written description requirement.

The rejection of claim 6 for use of the phrase "accelerator" rather than "heparin" is respectfully traversed. First, the AT binding partner is now limited to thrombin, and those skilled in the art will be well aware of how to accelerate the thrombin-AT reaction. Additionally, it is well known that other variables such as salt concentration, type of salt, and pH of the composition can each serve to accelerate the thrombin-AT interaction. As the claims are now cast in terms of thrombin rather than an AT binding partner generally, one skilled in the art will know how to adjust these variables to optimize the performance of the test.

With respect to claim 8, as the AT binding partner is now recited as "thrombin," those skilled in the art will be able to identify antagonists to the accelerator for the thrombin-AT reaction.

With respect to the rejection at page 9, paragraph 10 of the Office Action, claim 1 has been amended to clarify that a determination of the amount of free thrombin is performed in step (b) of the claim.

With respect to the rejection at page 9, paragraph 11, of the Office Action, the word "excess" has been deleted from the claim, thereby obviating this ground of rejection.

As all grounds of rejection under 35 U.S.C. § 112, first paragraph have been overcome, it is respectfully requested that these grounds of rejection be withdrawn.

Rejections Under 35 U.S.C. § 103

The rejection of claims 1-2, 4, 6-7, and 11 as obvious over Plattner et al. in view of Furatu, Morris et al, and Akhavan-Tafti et al. is respectfully traversed.

One aspect of the invention lies in the surprising discovery that it is possible to conduct two reliable determinations of free thrombin successively in one and the same sample, and by comparing the determinations to obtain an accurate determination of AT in the sample, despite the presence of a drug in the sample which otherwise would interfere and thereby render the determination inaccurate. Also, one skilled in the art would not have expected that it would have been possible to obtain an accurate determination of AT by comparing the two thrombin

measurements when the second thrombin measurement is made after the addition of the regent R3.

To the contrary, the skilled person upon reading Plattner et al., would have expected that a reliable comparison between the first and second determinations of free fractions of AT binding partner would not have been possible, due to the addition of the R3 reagent between the first and second determinations.

Specifically, in the present invention, only a *single determination of AT* is made, based on *two measurements of free thrombin in the same sample* but under different conditions. Plattner does not teach or suggest that free thrombin should be measured twice under different conditions to determine the amount of AT in a sample. Nor does Plattner suggest that it is possible to determine the amount of AT in a sample when an interfering factor such as a drug is also present. In Plattner, the free thrombin is measured only *after* there has been a heparin-accelerated thrombin-AT interaction, not before. As explained in Plattner at col. 6, line 60 – col. 7, line 3, excess thrombin is added to a sample in the presence of heparin, such that excess thrombin is free to hydrolyse a colorless chromogenic substrate. When the substrate is cleaved by thrombin the substrate releases in the absorbance spectrum, such that by monitoring the color development one can follow the turnover of the substrate by thrombin. The amount of AT-III and the amount of color produced are inversely proportional, such that the level of AT-III can be determined. It may be seen that in the method of Plattner all the color determinations are made under the same conditions.

Contrary to the Examiner (Office action page 10, last line – page 11, line 1), Plattner does not teach adding a third reagent R3 to change the conditions under which thrombin is measured; thrombin is only measured as a function of the amount of the chromophore produced, after the addition of heparin, from which the amount of AT can be derived.

As the Examiner correctly notes, Plattner et al. differs from the claimed invention in that it fails to specifically teach conducting two measurements of the same substance at different times and under different conditions in a single reaction mixture. With regard to the other cited references, applicant points out the claims as now amended are limited to detection of AT using thrombin, and none of the secondary references relates to AT or thrombin. The Furatu reference does not teach the analysis of a single substance by two separate measurements in a single reaction mixture. Instead, Furatu in the paragraph spanning pages 3-4, teaches the analysis of a "first analysis item," then adding a reagent to measure a "second analysis item," the calculation

of the concentration of the "second analysis item" being corrected to account for the amount of reagent added. This does not teach comparative analyses of any single analyte, and certainly not of an AT binding partner under different reaction conditions to determine AT. In other words, Furatu teaches separate measurements to measure different substances, not separate measurements of the same substance under different conditions. Similarly, the Morris reference teaches performing a test on a sample to determine the presence of ANA, and then performing other tests on the same sample to confirm the presence of a disease. Morris does not teach taking the difference between any two tests of a single analyte under different conditions to obtain a quantitative determination of a substance with which the analyte reacts. The Akhvan-Tafti reference also teaches taking the measurements of two different analytes at a single time, not using the difference between two measurements at different times and under different conditions on the same sample to determine a single analyte.

In other words, none of the cited art teaches or suggests the essence of the present invention, namely, the measurement of an analyte, in this case thrombin, under two different reaction conditions, namely without and with the presence of a reaction accelerator, on a single sample in a single reaction vessel to provide a quantitative determination of another substance in the reaction mixture, in this case AT.

As applicant has noted, the previously presented Hickey monograph (2008 GTH Congress (Congress of Gesellschaft für Thrombose-und-Hämostaseforschung, held February 20-23, 2008, Wiesbaden, Germany)) shows that the problem of the presence of the drug Leprudin as an interfering factor in determinations of AT still had not been solved. If employing the "creative step" of the present invention would have been obvious to those skilled in the art, those steps would have been so employed by the time of the GTH 2008 Congress. The "creative step" that the Examiner dismisses as obvious is in fact one that has not yet been employed by others to solve this long-recognized need in the art.

The Examiner's statement at page 21 that "Applicant has not advanced sufficient evidence that this problem was not already solved by others before the invention by Applicant" is respectfully not understood, as the problem discussed in the Hickey monograph shows exactly that. Further, the Examiner's citation of the statement at paragraph [0006] of the present specification is not understood. That statement says that the problem of drug interference that had been experienced with the use of thrombin can be solved with the use of factor Xa instead of thrombin, because drugs that interfere with factor Xa were not commonly used. That does not

teach one how to avoid the problem of drug interference when thrombin is used; the Hickey monograph demonstrates that that problem still exists. Furthermore, the next sentence in that paragraph [0006] of the specification points out that other drugs are currently being developed that are expected to be interfering factors with Xa, so that it is also necessary to provide a method that will enable quantitative AT determinations in the presence of Xa interfering factors.

The rejection of claim 10 as obvious over Plattner et al. in view of Furatu, Morris et al., and Akhavan-Tafti and further in light of Gitel is respectfully traversed. Gitel is cited as teaching that heparin is an AT binding partner. In the present invention, heparin is not used as an AT binding partner, but as an accerator of the thrombin-AT reaction. Claim 10 recites that R3 can comprise additional AT binding partner; in the example of the application, that additional binding partner is additional thrombin. Accordingly, Gitel taken in combination with the other references does not render claim 10 obvious.

The rejection of claims 8 and 9 as obvious over Plattner et al. in view of Furatu, Morris et al., and Akhavan-Tafti and further in light of Exner is respectfully traversed. Exner is cited as teaching that polybrene is a heparin antagonist. The Examiner states that it would have been obvious to use polybrene in the step of measuring the progressive anti-thrombin activity as taught by Plattner. But in Plattner the step of measuring the progressive anti-thrombin activity is specifically conducted in the presence of heparin to accelerate the thrombin AT interaction; i.e., Plattner et al. specifically teach the addition of heparin to the reaction mixture, it would not be obvious to add an antagonist for a component that is specifically added. Accordingly, claims 8 and 9 of the present application are not obvious over the cited art.

In view of the foregoing, a Notice of Allowance is respectfully requested.

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